

Current Trials on MDRO Containment

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Disclosures: None

Strategies to Reduce MDROs

Majority of efforts directed at MRSA/VRE

- Vaccinate
- Contact precautions
- Active screening
- Enhanced cleaning
- Decolonization
- Antibiotic rotation

Vaccination Trials

StaphVAX Trial

- *S. aureus* conjugate vaccine
 - Capsular polysaccharides 5 and 8
- Tested on 1,804 patients on hemodialysis
- Robust early antibody response

Shinefield H et al. *New Engl J Med* 2002; 346:491-96

StaphVAX Trial

TABLE 4. GEOMETRIC MEAN LEVELS OF ANTIBODIES SPECIFIC FOR *STAPHYLOCOCCUS AUREUS* TYPE 5 AND 8 CAPSULAR POLYSACCHARIDES.*

TIME OF EVALUATION	VACCINE GROUP			PLACEBO GROUP		
	NO. OF PATIENTS	TYPE 5	TYPE 8	NO. OF PATIENTS	TYPE 5	TYPE 8
		$\mu\text{g/ml}$			$\mu\text{g/ml}$	
Before injection	892	5.9	8.6	910	5.7	8.6
Week 6	884	230.0	206.0	900	5.6	8.6
Week 26	838	120.0	100.0	859	5.8	8.9
Week 54	763	74.2	64.5	776	5.7	8.9
Week 67	507	78.1	65.8	512	6.2	9.4

StaphVAX Trial

TABLE 2. CUMULATIVE NUMBER OF PATIENTS IN WHOM *STAPHYLOCOCCUS AUREUS* BACTEREMIA DEVELOPED AND EFFICACY OF THE VACCINE.*

WEEKS AFTER INJECTION	VACCINE GROUP		PLACEBO GROUP		EFFICACY (95% CI)	P VALUE
	NO. INFECTED	PERSON- YEARS	NO. INFECTED	PERSON- YEARS		
					%	
10	4	135.2	5	138.0	18 (−28 to 84)	1.0
20	6	300.6	13	306.6	53 (−33 to 85)	0.17
30	8	461.9	22	469.7	63 (14 to 86)	0.02
40	11	618.9	26	627.0	57 (10 to 81)	0.02
50	25	766.5	34	775.3	26 (−28 to 58)	0.30
54	27	818.4	37	827.4	26 (−24 to 57)	0.23
91	37	1165.0	49	1161.6	25 (−18 to 52)	0.24

StaphVAX Trial

- Provided partial immunity
 - Initially thought to be protective till 40 weeks
 - Failed to verify effect with serial inoculations
 - >3,500 person trial – Phase III failed

Shinefield et al. *New Engl J Med* 2002; 346:491-96
Fattom et al. *Vaccine* 2004;23(5):656-63

Vaccines in Clinical Trials

Candidate	Sponsor	Rationale	Status
StaphVAX	Nabi Biopharmaceuticals	CP5, CP8	Phase III failed
Veronate	Inhibitex	Cell Wall Adhesins	Phase III failed
v710	Merck	Monovalent ?Iron Surface Determinant B?	Phase III clinical trials
SA3Ag	Pfizer/Wyeth	Tri-valent CP5, CP8, rClfAm	Phase I Early 2011
Pentastaph	GSK (Nabi)	CP5, CP8, cell wall antigen 336, PVL and α toxin	Phase 1 3 of 4 milestones already met

Value

- Prevent infection among carriers
 - Reducing carriage
 - Reducing acquisition
- Moderate efficacy highly valuable
- Potential long term benefit

Strategies to Reduce MDROs

- Vaccinate
- Contact precautions
- Active screening
- Enhanced cleaning
- Decolonization
- Antibiotic rotation

Contact Precautions

Common Guidelines

- Contact Precautions
 - Hand hygiene to enter
 - Gown and glove to enter room/contact
- Cohorting
 - Single room or
 - Rooming with other MDRO patients

Contact Precautions

- Dozens of studies
- Successful response to outbreak conditions
- Successful response to endemic MDROs
- All observational
- Overall, precautions favored, but studies not definitive

Contact Precautions

- Widely used and internationally recommended
- Logical benefit
- Final answer unknown
 - Isolated effect difficult to study
 - Quantitative effect difficult to study
 - Time window to randomize may have passed
 - Research focus is now on other interventions

Universal Glove & Gowning Study

- Recruiting (US)
- Cluster randomized trial of 18+ ICUs
- **Arm 1:** Routine contact precautions
- **Arm 2:** Universal contact precautions
- **Study Period:** Apr 2011 – Mar 2012
- **Outcomes**
 - MRSA, VRE ICU acquisition
 - ICU associated infection rates

AHRQ funded, Task Order PI: Anthony Harris , ACTION network (Yale)

Strategies to Reduce MDROs

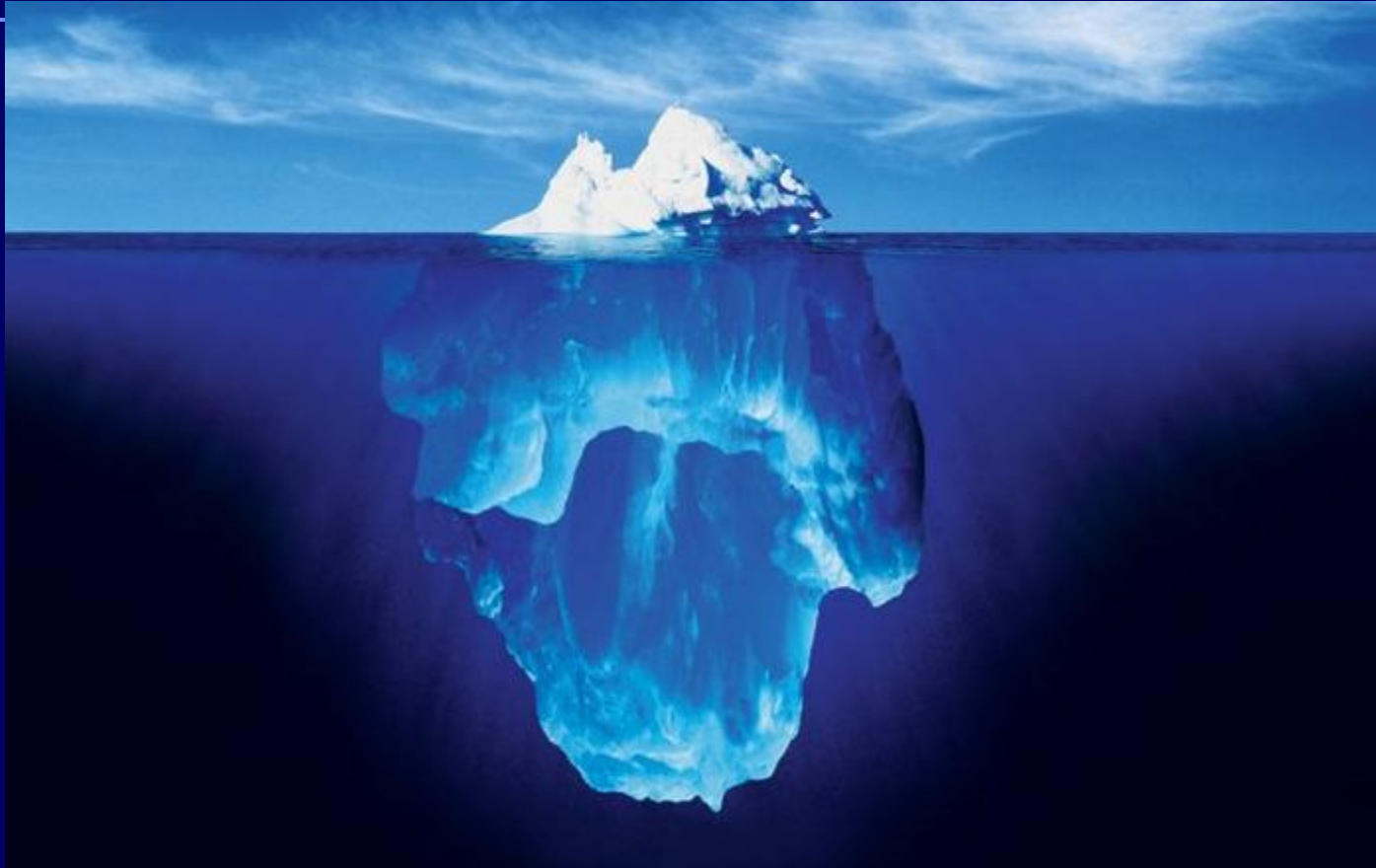
- Vaccinate
- Contact precautions
- **Active screening**
- Enhanced cleaning
- Decolonization
- Antibiotic rotation

Active Screening & Isolation

The Iceberg Phenomenon



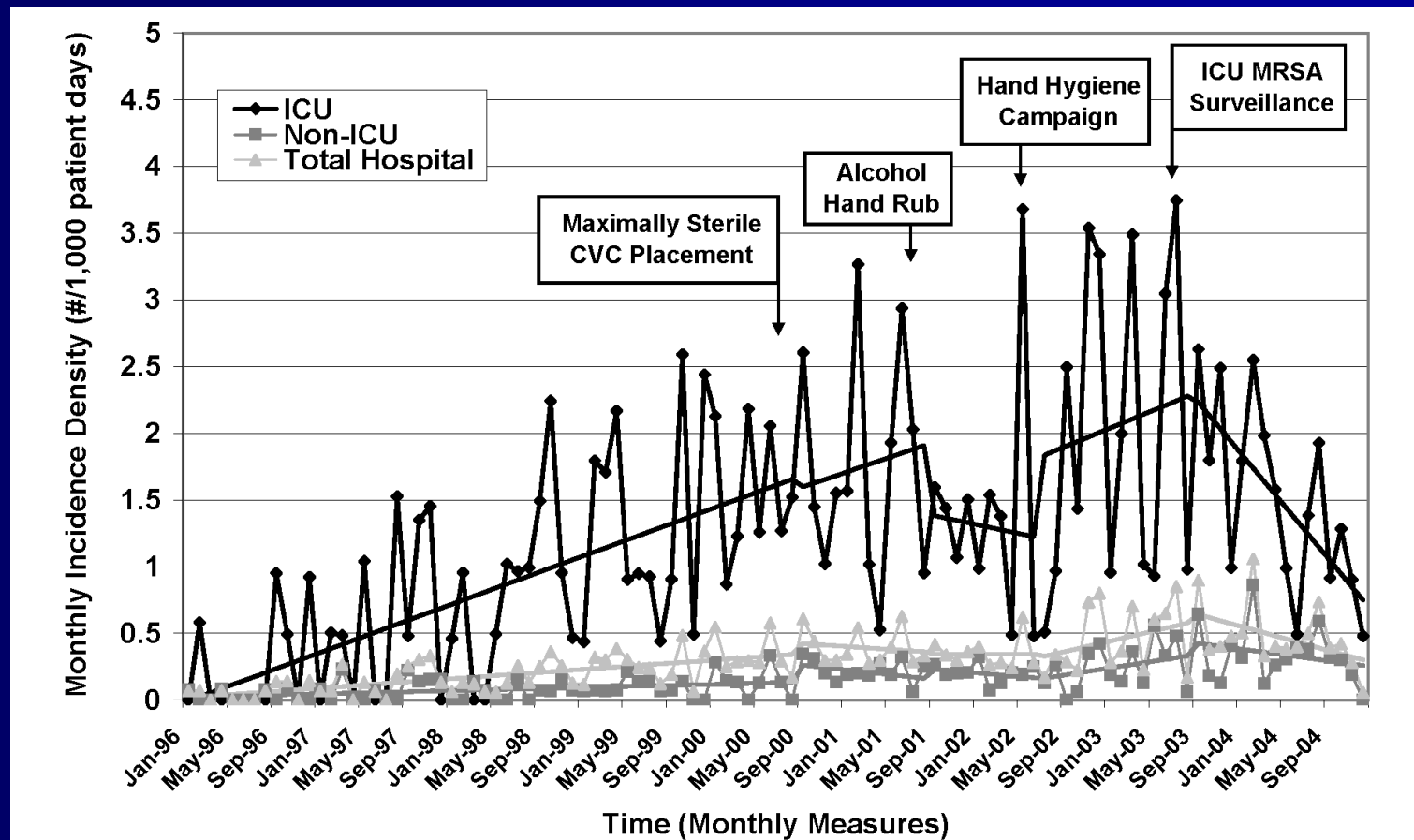
The Iceberg Phenomenon



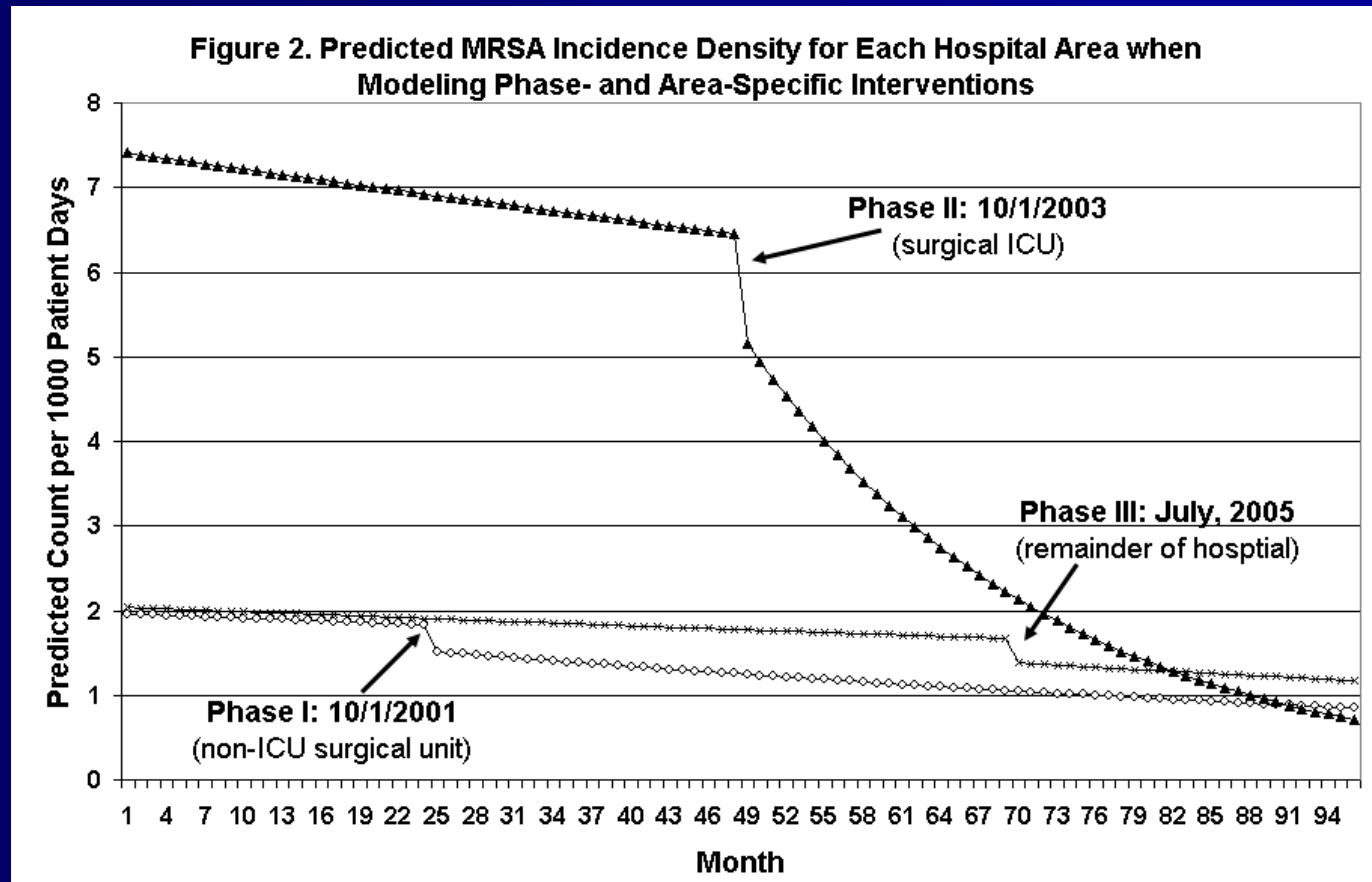
Value of Active Surveillance

- Knowledge of iceberg
 - Increases detection
 - Increases awareness
 - Corrects misclassification
- Rapid isolation
 - Contact precautions
 - Prevents transmission

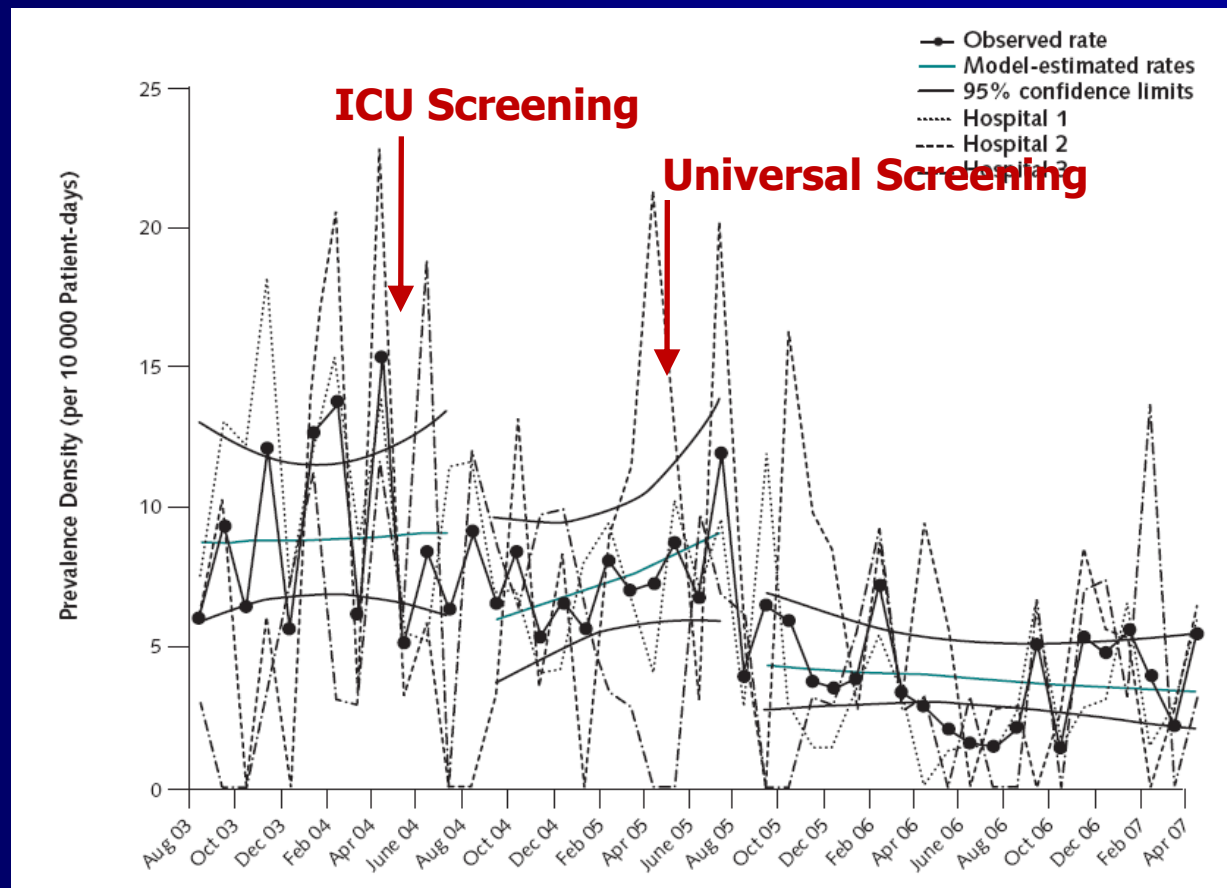
ICU Screening & Isolation Impact on MRSA Bacteremia



Phased In Screening & Isolation Impact on MRSA Acquisition

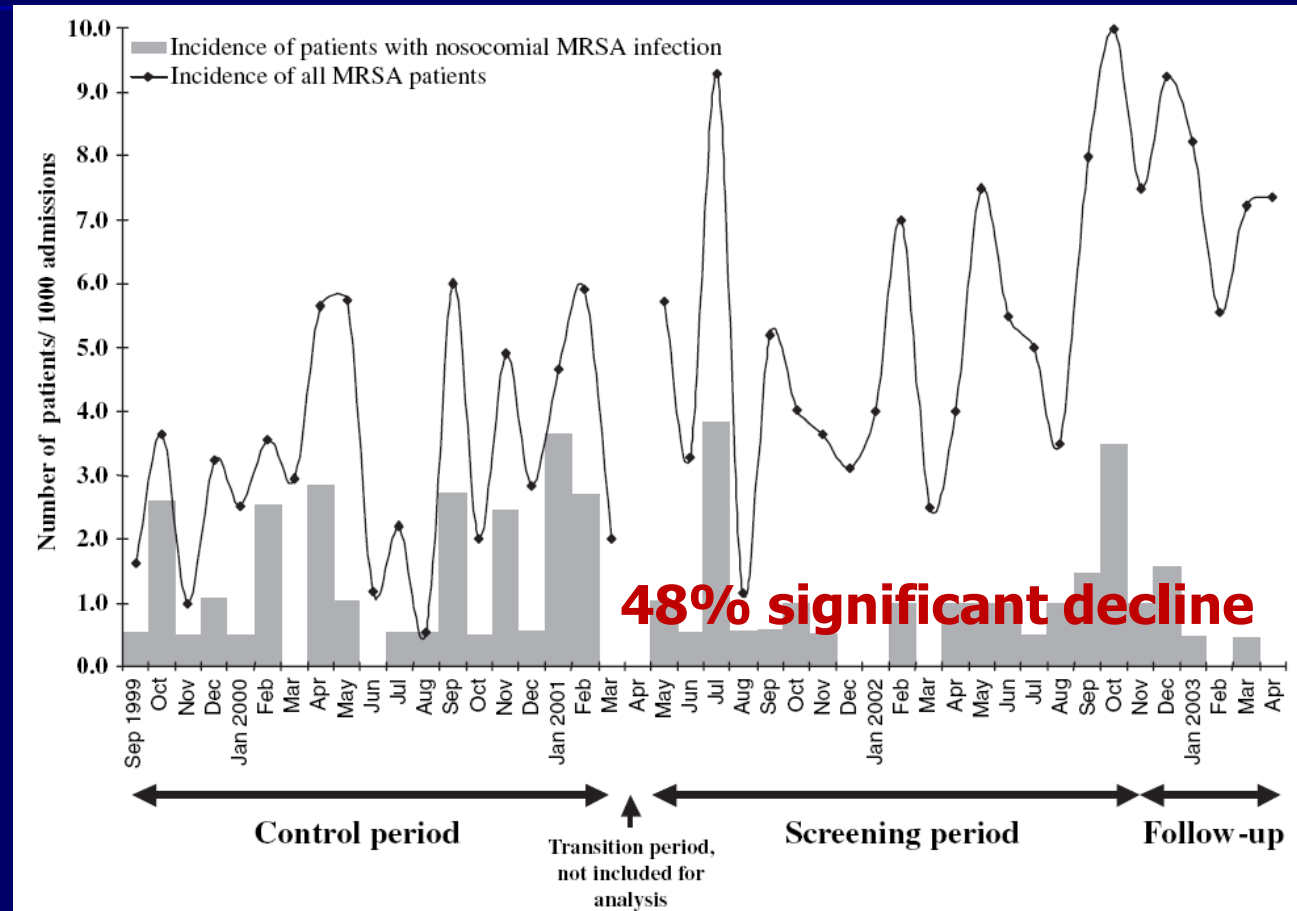


Housewide Screening & Isolation Impact on MRSA Infections



Evanston Northwestern Health Care
Robicsek et al. Ann Int Med 2008;148:409-18

High Risk Screening & Isolation Impact on MRSA Infection

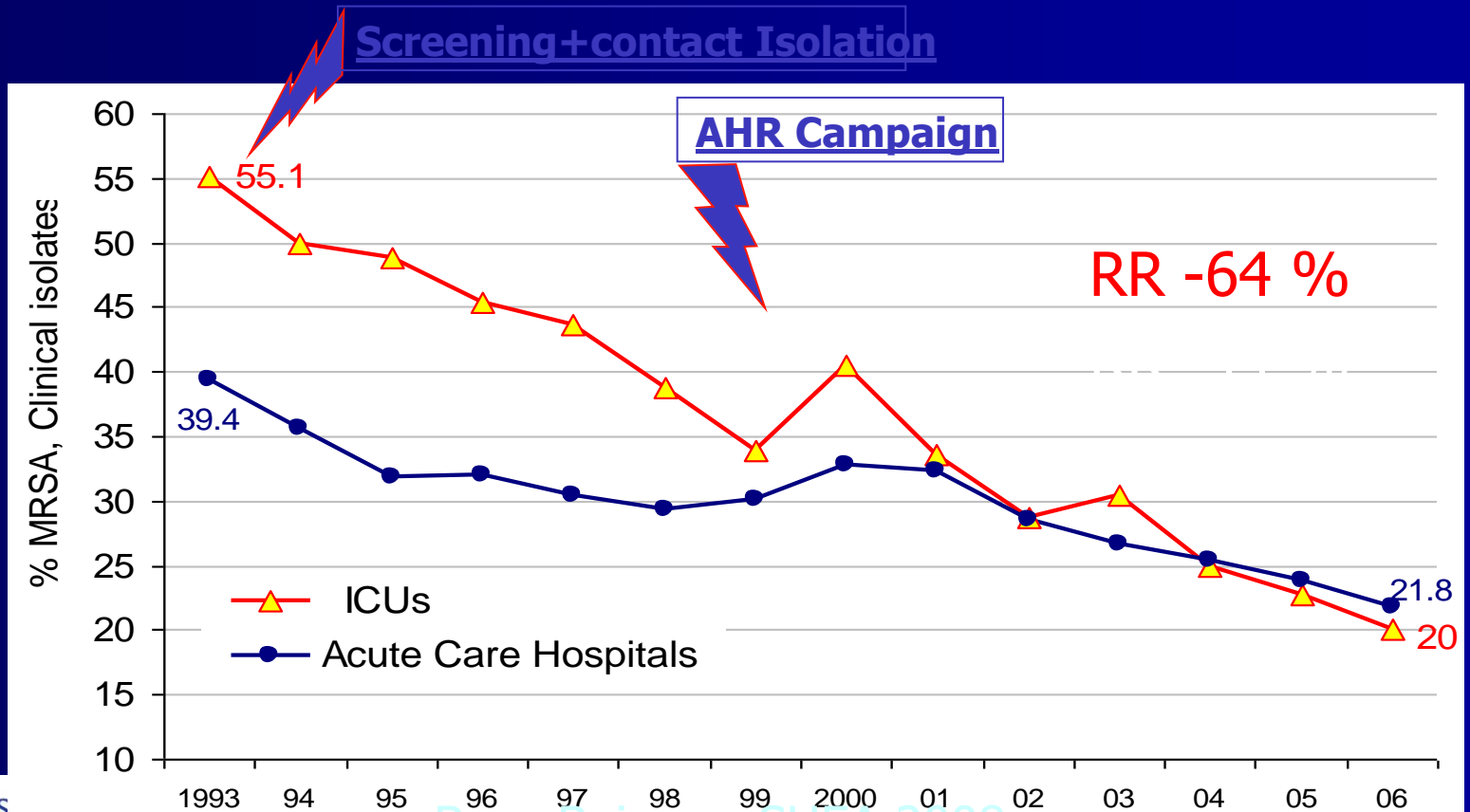


Klinikum im Fredrichshain, Berlin Germany
Wernitz et al. Clin Microbiol Infect 2005;11;457-65

Trends in MRSA

Paris 1993 - 2006

MRSA Prevalence among *S.aureus* clinical samples



STAR ICU Trial

- Strategies to reduce Transmission of Antimicrobial Resistant bacteria in ICUs
- Cluster RCT evaluating intensive precaution measures to prevent MDROs (C Huskins, USA)
- Two ICU Arms
 - Universal gloving, plus screen and isolate
 - Routine care (but screen without results)

STAR ICU Trial

- Sample Size
19 hospitals, 15 US states
- Study Period
2005-6
- Outcome
Incidence of MRSA and VRE acquisition
MRSA and VRE bacteremia

STAR ICU Trial

- Major trial design flaw
 - All screens sent to central laboratory (CDC)
 - Screening results returned on average 2 days longer than average LOS in ICU
 - Effectively a study of universal gloving
- Outcome
 - No substantial benefit (prelim report)
 - Final publication forthcoming (NEJM)

MOSAR Trials

Mastering hOSpital Antibiotic Resistance

- European consortium
- Three trials
 - Intensive Care Units (M Bonten, UMCU, NL)
 - Surgical Care Units (S Harbarth, UNIGE, CH)
 - Rehabilitation Centers (Y Carmeli, TASMC, IL)
- Evaluation of acquisition of MDROs

MOSAR Trials

Mastering hOSpital Antibiotic Resistance

- The Intensive Care Unit Trial
- Objective
 - Compare incremental effects of:
 - Enhancing basic infection control measures
 - Active surveillance by culture + isolation
 - Active surveillance by PCR + isolation
- Outcomes
 - ICU associated acquisition MRSA, VRE, ESBL
 - ICU-associated MRSA, VRE, ESBL bacteremia
 - ICU stay, hospital stay, mortality

MOSAR Trials:

The Intensive Care Units Trial

- 13 adult ICUs
- Cluster Randomized
- Launch: May 2008
- Phase 1: Baseline (6 mo)
- Phase 2: (All sites, 6 mo)
 - Hand hygiene campaign
 - Daily CHG bathing
- Phase 3 (12 mo), randomized for active surveillance
 - Arm 1: Chromagar for MRSA/VRE; no active ESBL detection
 - Arm 2: PCR for MRSA/VRE; chromagar for ESBL



MOSAR Trials:

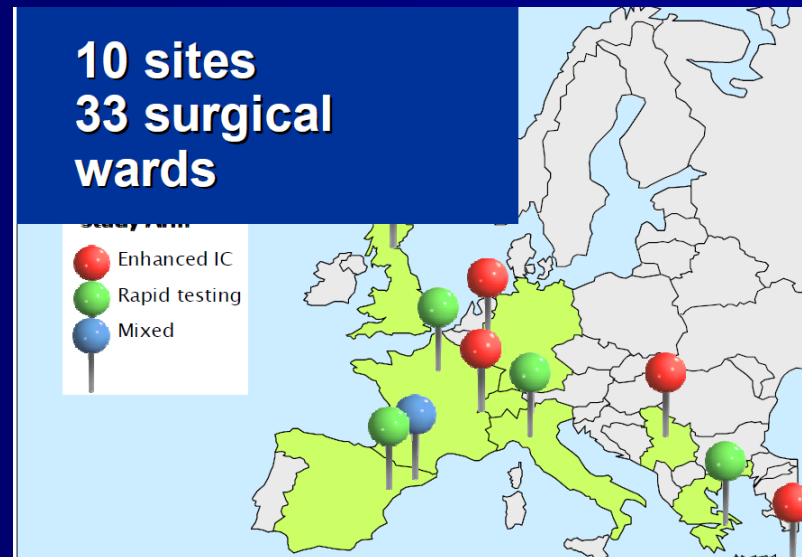
The Intensive Care Units Trial

- Data collection will complete March 2011
- >11,000 patients, >110,000 patient days
- Final analyses: Early 2012
- **Critical value**
 - Value of screening over universal CHG bathing
 - Value of PCR over conventional screening

MOSAR Trials

Mastering hOSPital Antibiotic Resistance

- The Surgical Units Trial
- Objective
 - Compare basic infection control measures vs active screening and isolation in non-ICU surgical wards



Options to Reduce MDROs

- Vaccinate
- Contact precautions
- Active screening
- Enhanced cleaning
- Decolonization
- Antibiotic rotation

Enhanced Cleaning

Bacteria on a Pen Tip



PRIMO Trial

Prevention of **I**nfection caused by
Methicillin or **O**xacillin resistant *S. aureus*

- RCT to Prevent Recurrent CA-MRSA Infection
- 2x2 Clinical Trial (L Miller, Harbor UCLA, USA)
 - No intervention
 - Household cleaning intervention (topical ETOH)
 - Decolonization (7d mupirocin, 14d CHG bathing)
 - Household cleaning + Decolonization

NIH- funded; Clinicaltrials.gov: NCT00560599

PRIMO Trial

Decolonization vs Cleaning

- **Sample Size**
350 households with recent CA-MRSA infection
- **Outcome**
MRSA infection within 52 weeks
- **Study Period**
2007-2010, completed, analysis pending

Options to Reduce MDROs

- Vaccinate
- Contact precautions
- Active screening
- Enhanced cleaning
- Decolonization
- Antibiotic rotation

Decolonize

Value of Decolonization

- Benefits prevalent cases
- Infection risk in known carriers
 - 1 in 3 in critically and chronically ill
 - 1 in 9 among nursing home residents
- Most common regimen for MRSA
 - Mupirocin for nasal reservoir
 - Chlorhexidine for skin decontamination
 - Avoids resistance to treatment agents

Mupirocin

- Short-term mupirocin highly effective ¹
 - 90% elimination of MRSA at 1 week
 - 60% prolonged elimination
- 1%-7% ² resistance over time

¹ Ammeriaan HS et al. Clin Infect Dis 2009;48(7):922-30

² Robicsek A et al. Infect Control Hosp Epidemiol 2009;30(7):623-32

Chlorhexidine

- Topical cleansing agent, over the counter
- Used in healthcare for >50 years
- Marked reduction in skin/room bacteria
- Commonly used for
 - MRSA decolonization
 - Pre-operative bathing/showering
 - Skin prep before central lines/operations

Chlorhexidine and Bacteremia

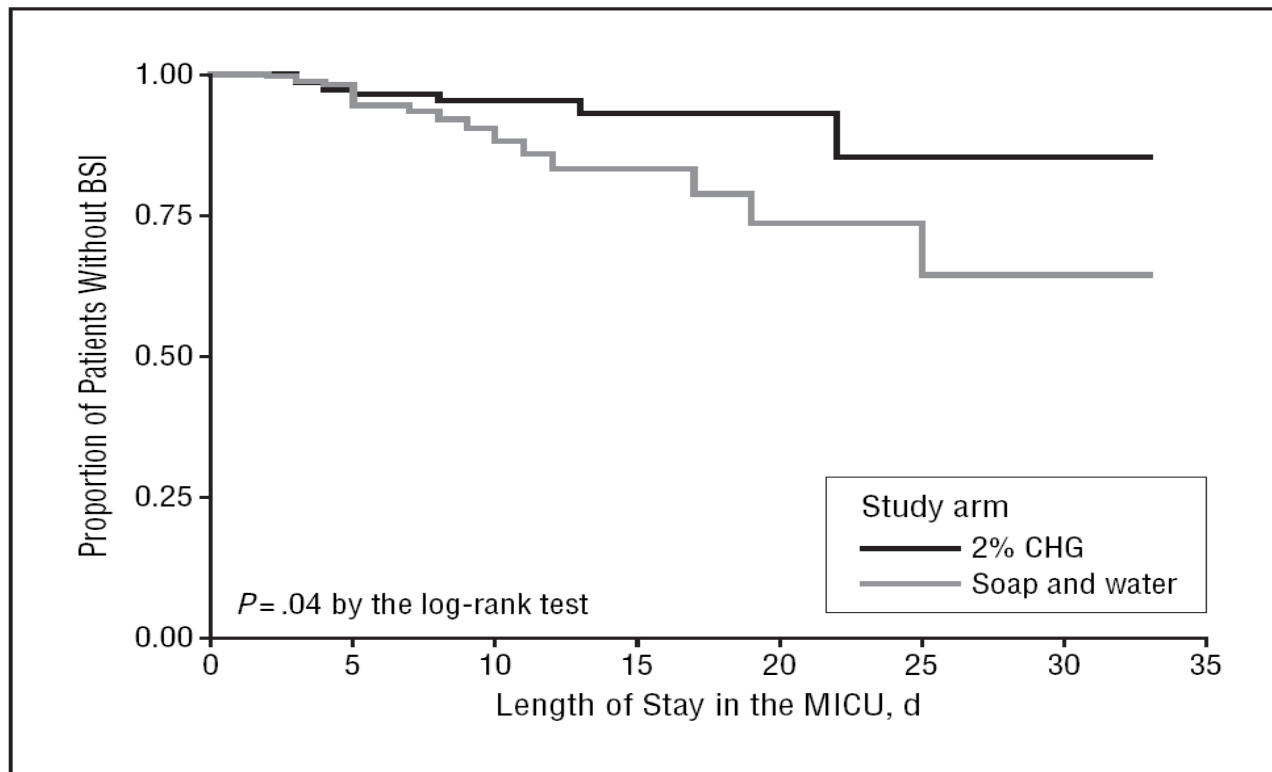
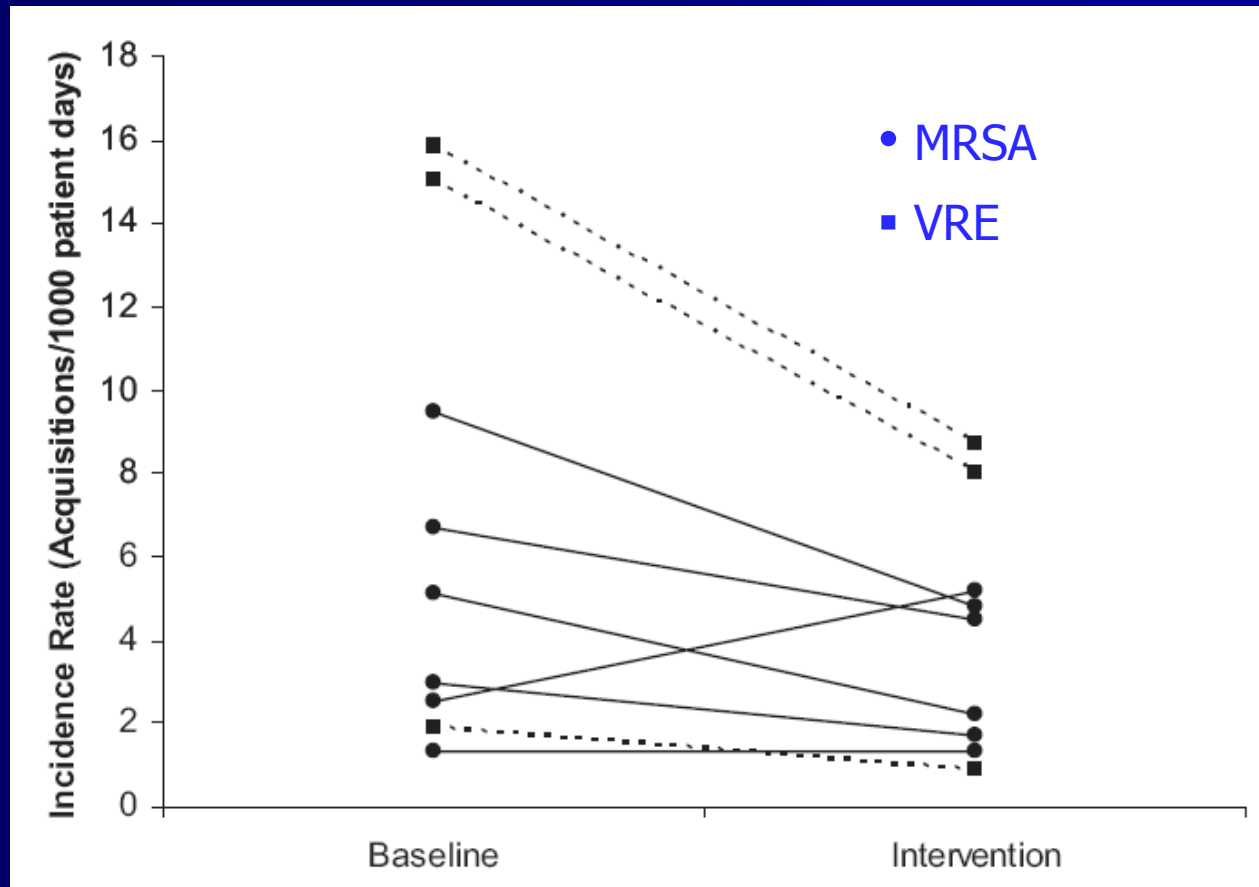
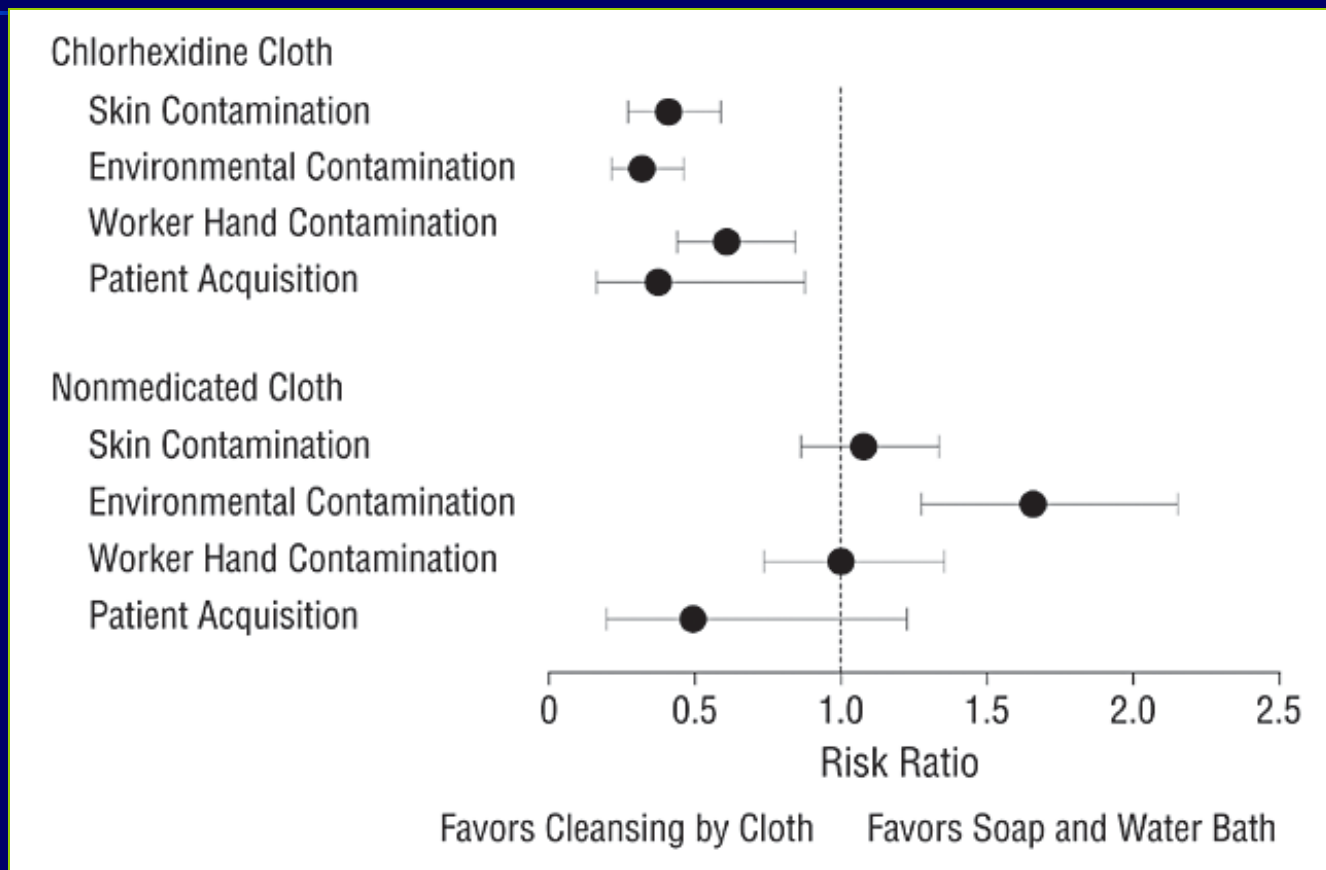


Figure 2. Kaplan-Meier survival curve for occurrence of bloodstream infection (BSI) by study arm. CHG indicates chlorhexidine gluconate; MICU, medical intensive care unit.

Multi-Center ICU Study of CHG



Risk Ratios for Skin Contamination and Environmental or Health Care Worker Contamination by or Patient Acquisition of VRE



The REDUCE MRSA Trial

A multi-center cluster randomized study

AHRQ funded; [Clinicaltrials.gov NCT00980980](https://clinicaltrials.gov/ct2/show/study/NCT00980980)

REDUCE MRSA

Randomized Evaluation of Decolonization vs. Universal Clearance to Eliminate MRSA

Susan Huang, MD MPH

Richard Platt, Ed Septimus, John Jernigan, Jason Hickok, Julia
Moody, Jonathan Perlin for the REDUCE MRSA Working Group

CDC Prevention Epicenters
Harvard Pilgrim Health Care
Hospital Corporation of America



The REDUCE MRSA Trial

- 3-Way Cluster Randomized Trial (US)
 - Randomizes whole hospitals (all adult ICUs)
 - 42 hospital participants/74 ICUs
 - 16 states
- Arm 1: Routine Care
 - Screen and isolate only
- Arm 2: Targeted Decolonization
 - Screen, isolate, and decolonize if MRSA+
- Arm 3: Universal Decolonization
 - Stop screening, isolate known MRSA+, decolonize all

REDUCE MRSA Trial Outcomes

■ Main Outcome

- Any clinical MRSA isolate attributed to an ICU or post-ICU (cultures attributed to unit 2d prior)

■ Secondary Outcomes

(ICU, post-ICU, and hospital-wide analyses)

- Blood and urine MRSA infections
- Blood and urine infections, all pathogens
- Antibiotic resistance to mupirocin or chlorhexidine

Trial Status and Timeline

- Trial duration April 1, 2010 – Sept 30, 2011
- >95% compliance in all facilities, every arm
- Final results expected in 2012



CHANGING LIVES BY ERADICATING ANTIBIOTIC RESISTANCE

A randomized clinical trial
Southern California, USA

AHRQ funded; [Clinicaltrials.gov NCT00980980](https://clinicaltrials.gov/ct2/show/study/NCT00980980)

Project CLEAR

- RCT to prevent MRSA infections among carriers in the year following discharge
 - Arm 1: Standard of Care Hygiene Education
 - Arm 2: Education + Decolonization
 - 5 days application twice a month for 6 months**
 - ❖ Mupirocin to bilateral nares
 - ❖ Chlorhexidine bathing
 - ❖ Chlorhexidine mouthwash

Project CLEAR

- Sample Size
 - 1700
- Follow up
 - 1 year
 - 4 clinic visits with serial cultures
- Medical records requested for
 - All hospitalizations
 - Any clinic visit for possible infection

Project CLEAR Recruitment

- **Recruitment**

Adults at discharge from hospitals or admission to nursing homes in Southern California
(Orange County and Southern Los Angeles)

- **Outcomes**

MRSA infection, rehospitalization 1 yr post-discharge
Increased mupirocin or chlorhexidine resistance

- **Study Period**

Jan 2011-Mid 2013

Options to Reduce MDROs

- Vaccinate
- Contact precautions
- Active screening
- Enhanced cleaning
- Decolonization
- Antibiotic rotation

SATURN ICU Trial

Impact of **S**pecific **A**ntibiotic **T**herapies on the prevalence of h**U**man host **R**esista**N**t bacteria

- Randomized cross over trial
- **Arm 1:** Fast rotation
 - Every other patient rotates antibiotics
 - cephalosporins, pip-tazo, carbapenems
- **Arm 2:** Slow rotation
 - Every 1.5 months, unit rotates antibiotic

Clinicaltrial.gov: NCT01293071

SATURN ICU Trial

■ Primary Outcome

- Prevalence of antibiotic resistant GNR

■ Secondary Outcome

- Acquisition of antibiotic resistant GNR
- Antibiotic resistant GNR bacteremia

■ Study Period

- Spring 2011 - Jan 2013

Conclusions

- **MDROs are a national priority**
 - Increasing carriage and disease prevalence
- **Need answers for containment**
 - Staph vaccine trials
 - Universal Gown & Gloving Trial
 - MOSAR Trials
 - PRIMO Study
 - REDUCE MRSA Trial
 - Project CLEAR
 - SATURN

Questions?

